Biologics and biomarkers

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ABSTRACT

Introduction: *Asthma is a chronic airway disease that has a substantial impact on increased health-care utilization, including a substantive impact on quality of life and morbidity. Biologics are considered in patients with severe asthma and who have poor baseline symptom control and recurrent exacerbations that require emergency department visits, hospitalizations, and prolonged steroids courses. With six different biologics currently being available to treat severe uncontrolled asthma, the choice of which biologic to proceed with is usually based on the biomarkers and clinical characteristics, including comorbidities. The lack of response in some patients suggests that there may be an interplay of more complex immunologic pathways that are contributing to the severity of asthma in said patients. In this review, we attempted to highlight what we know about the various biomarkers used in the management of asthma, while also shedding light on what is yet to be known and understood. We also briefly delved into the various clinical characteristics in patients with severe asthma that may influence the choice of one biologic over the other.*

Methods: *An extensive PubMed search was conducted by using the search terms benralizumab, dupilumab, mepolizumab, and omalizumab. Additional search terms included asthma biomarkers, exhaled nitric oxide, blood and sputum eosinophil counts, total IgE levels, comorbidities, and predictors of response. In general, all searches dated back ~10 years, with the exception of the omalizumab data.*

Discussion: *Although there is no doubt that biomarkers have a role in the management and stratification of asthma, we must understand that there are several nuances to using them when evaluating a patient and when making decisions on the biologic of choice and subsequent monitoring of these patients. There are still substantial gaps in our knowledge of how they should be reliably used in asthma management, and it is important to understand the limitations to avoid overestimating the extent of their utility.*

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Asthma is a chronic airway disease with a high prevalence in all age groups worldwide, which affect ~334 million people. It is the most common chronic disease in children, and overall has a substantial impact on increased health-care utilization, including a significant impact on quality of life and morbidity.[1] The advent of biologics for the treatment of asthma has heralded the age of personalized medicine in the management of severe asthma. With six different biologics currently being available to treat severe uncontrolled asthma, the choice of which biologic to proceed with is usually based on the biomarkers and clinical characteristics, including comorbidities. The lack of a response in some patients suggests that there may be an interplay of more complex immunologic pathways that are contributing to the severity of asthma in said patients. In this review, we attempted to highlight what we know about the various biomarkers used in the management of asthma, while also shedding light on what is yet to be known and understood. We also briefly delved into the various clinical characteristics in patients with severe asthma that may influence the choice of one biologic over the other. We limited the focus on the five commonly used biologics due to their subcutaneous route of administration and did not discuss reslizumab because it is not often used in clinical practice due to only an intravenous formulation being available.

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METHODS

An extensive PubMed search was conducted by using the search terms benralizumab, dupilumab, mepolizumab, omalizumab, and tezepelumab. Additional search terms included asthma biomarkers, exhaled nitric oxide, blood and sputum eosinophil counts, total immunoglobulin E (IgE) levels, comorbidities, predictors of

response. Generally, all searches dated back ~10 years except for the omalizumab data for which we did not put a time limit for data search.

Biomarkers in Asthma

Asthma biomarkers are currently used in phenotyping and selecting treatment options, and prognostication, with a questionable role in monitoring the response to treatment.[2] The most convenient and widely used biomarkers are peripheral blood eosinophil count, fractional exhaled nitric oxide (FeNO), and total serum IgE. Although the sputum eosinophil count could potentially provide a better inflammatory profile of the airway than other compartments, it is cumbersome, nonreproducible from laboratory to laboratory, and more invasive than checking the above biomarkers. Due to the lack of standardized protocols for processing the samples and the other issues detailed above, sputum analysis was not used in the development of current antibody-based therapies and is primarily used in the research setting. We will therefore be discussing peripheral blood eosinophil count, FeNO, and total serum IgE level in further detail in this article.

There is no doubt that there is a role for some of these biomarkers in the management of severe asthma. However, there are some limitations that are common to all of these biomarkers. All the biomarkers that are currently in use in clinical practice are directed toward type 2 (T2) inflammatory asthma. At present, we do not have any biomarkers specific for T2-low asthma, and there is a lot of research and work yet to be done to characterize T2-low disease because, in most definitions, it is primarily defined by the absence of T2 markers rather than its own defining features. Another limitation is that the levels of FeNO, blood eosinophils, and total IgE can fluctuate over time in the same patient. Earlier studies have shown that blood eosinophil and FeNO levels can naturally fluctuate in patients with asthma and the general population. Medications, *e.g.*, corticosteroids, can also lower these levels.[2,3]

Peripheral Blood Eosinophil Count

Compared with healthy controls, patients with asthma have higher levels of eosinophils in their bronchoalveolar lavage and peripheral blood.[4] Although, eosinophil biology is rather complex and beyond the scope of this review, it is well understood that eosinophils contribute to asthma pathophysiology by releasing various cytokines and toxic granules that can contribute to airway hyperresponsiveness, mucous production, tissue damage, and remodeling.[5]

Whether the peripheral blood eosinophil count can be used as a surrogate marker for sputum eosinophils is a question that remains fully unanswered. A study by Fowler *et al.*[6] evaluated 163 patients, most of whom were receiving high-dose inhaled or systemic corticosteroids, which demonstrates that a blood eosinophil count > 0.45×10^9 cells/L could predict sputum eosinophilia (>2%) in 9 of 10 patients. However, Hastie *et al.*[7] had contrary findings in their study of 328 patients. Although there was a significant association between sputum eosinophil percentages and blood eosinophil counts, the latter did not accurately predict the former. A 2015 meta-analysis that included 2405 patients showed that, to detect a sputum eosinophil count of >3%, blood eosinophils had a sensitivity and specificity of 71% and 77%, respectively, which suggests that blood eosinophils may have moderate diagnostic efficacy in serving as a surrogate for sputum eosinophil count.[8] Regardless, all the pivotal trials performed for approval of current asthma biologics therapies were performed by using peripheral blood eosinophil counts due to the ease and reproducibility of obtaining baseline and subsequent levels through blood draws as opposed to sputum or bronchoalveolar lavage.

There are several studies in the literature that support the role of blood eosinophil count in predicting future risk of asthma exacerbation. In a United Kingdom cohort study that included > 130,000 patients with asthma, it was noted that patients with eosinophil counts > 400 cells/μL had a 1.4 times higher risk of severe asthma exacerbations than patients with counts of ≤400 cells/μL. The rate of exacerbations also progressively increased with increasing eosinophil counts.[9] A 2023 study by Bleecker *et al.*[3] investigated blood eosinophil counts of 718 patients in the placebo arm of the benralizumab trials, SIROCCO and CALIMA.[3] It was noted that 42% of the patients had high, 31% had low, and 27% had variable blood eosinophil counts. The high and variable blood eosinophil count groups had a higher mean number of exacerbations over 12 months compared with the patients with low blood eosinophil counts (1.34 and 1.31 exacerbations over 12 months versus 0.97). This again suggests that blood eosinophil counts have a significant predictive value in estimating the future risk of exacerbations.[3]

Apart from omalizumab, all the currently approved biologics for severe asthma had reported substantially better effectiveness in patients with eosinophilic asthma, as we discuss below. Blood eosinophil counts, however, have a very limited role in monitoring the response to biologics in the treatment of asthma. It can be low in patients who are not responding to anti–interleukin (IL) 5 agents and high in patients responding to anti–IL-4 agents, *e.g.*, dupilumab. The eosinophil count in these patients may only serve as an indicator of pharmacodynamic effect of the biologic agent and not the efficacy.

In the subgroup analysis of LIBERTY QUEST trial (phase III dupilumab study), it was noted that, in patients with a blood eosinophil count of ≥150 cells/mm^3, the dupilumab group had 35.6–67.4% lower risk of exacerbations, with the eosinophil count being directly proportional to the exacerbation risk reductions.

However, there was no significant difference between the exacerbation rates between the placebo groups and the patients on dupilumab, with an eosinophil count of <150 cells/mm^3.[10] Something to consider is that the patients who were eosinophilic in the placebo arm were also clinically worse, which may have exaggerated the difference between the groups because eosinophilic asthma is associated with worse asthma outcomes. *Post hoc* analysis of the LIBERTY QUEST trial[10] showed that peripheral blood eosinophils initially increased from baseline levels in patients on dupilumab, it eventually decreased slightly from baseline. The change in the eosinophils count from baseline levels with dupilumab was not associated with any significant reduction in risk of severe exacerbations but was associated with improved lung function.[11]

As with the LIBERTY QUEST trial,[10] in the Dose Ranging Efficacy And safety with Mepolizumab in severe asthma (DREAM) study with mepolizumab that investigated 616 patients who were treated with mepolizumab, exploratory modeling of various characteristics such as baseline blood eosinophil counts and asthma exacerbations in the previous year were explored. The researchers suggested that higher baseline eosinophil counts and exacerbations in the previous year improved the efficacy of mepolizumab. However, on looking closer, it can be noted that, in the mepolizumab group, the eosinophil count did not have a substantial effect on the number of exacerbations but rather the placebo group was doing significantly worse as the baseline eosinophil count increased.[12] Similar trends were also noted when looking closer at the pooled data from phase III SIROCCO[13] and CALIMA[14] trials on benralizumab.[15]

In a phase III double-blinded, placebo controlled trial on tezepelumab that randomized 1061 patients with severe asthma, it was noted that the tezepelumab treatment group had a >50% reduction in annual exacerbation rates (rate ratio of 0.44) and the reduction was directly proportional to the baseline blood eosinophil counts, with the patients with > 450 cells/μL having the highest benefit (77% versus 39% reduction for counts ≥450 cells/μL versus <150 cells/μL).[16] On looking at the supplemental data (Supplemental Fig. S8), it can be noted that the group with a FeNO value > 25 ppb and eosinophils > 300 cells/μL had the highest exacerbation reduction (77%) versus the group with eosinophils count > 300 cells/μL and lower FeNO level (39%) or with FeNO value > 25 ppb and lower eosinophils (53%), which suggest that both these biomarkers are synergistic in predicting a response.[16] As discussed in the context of mepolizumab in the paragraph above, when looking at Supplemental Figure S9 in the supplementary data of the tezepelumab phase III trial also showed that the placebo group had more exacerbations as the eosinophil count and FeNO level increased, which may have exaggerated the difference between the two groups.[16]

FeNO

In patients with eosinophilic and allergic asthma, IL-4 and IL-13 acts on respiratory epithelium and results in increased production of nitric oxide by induction of inducible nitric oxide synthase.[17]

A cross-sectional study with 74 patients with severe asthma by Couillard *et al.*[18] found that FeNO had a strong positive correlation with measures of airway inflammation such as IL-4, 5, eotaxin-3, thymus and activation-regulated chemokine, IL-33, thymic stromal lymphopoietin, and sputum eosinophils. However, blood eosinophils only correlated with serum IL-5 and not with any of the airway markers of inflammation.[18]

In a 2013 retrospective study by Hanania *et al.*[19] (analysis of the biomarker data from the EXTRA study)[20] that included 850 patients with severe persistent asthma on omalizumab, patients with high FeNO levels and peripheral blood eosinophil count were compared with subjects with lower levels of both. It was noted that, after 48 weeks of treatment with omalizumab, the exacerbation reduction rates were higher in the former group versus the latter group (FeNO: 53% versus 16%; absolute eosinophil count: 32% versus 9%).[17] However, the Prospective Observational Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab study,[21] a real-world prospective study, published several years later, looked at 801 patients with asthma who were started on omalizumab and found that, whereas omalizumab resulted in a significant reduction in exacerbation and hospitalization rates, improved ACT scores (Asthma Control Test Quality Metric, Inc., Johnston, Rhode Island), there was no clinically significant association with the biomarker status of the patients.[21]

In the LIBERTY QUEST trial,[10] a phase III study on dupilumab that randomized 1902 patients to receive dupilumab or placebo, patients with a baseline FeNO level of ≥25 ppb were noted to have an ~50% reduction in exacerbation risk compared with placebo. However, when this was compared with patients who had FeNO values of < 25 ppb, there was no significant difference from the placebo group. The data analysis evaluated a single biomarker response in relation to the exacerbation reduction not the interaction between FeNO and blood eosinophil count. The published report also showed the interaction between FeNO-high and FeNO-low groups in relation to high blood eosinophil groups as defined by a count > 150 cells/μL. Analysis of the reported data suggested that the highest exacerbation reduction (65%) was in the group with a FeNO value > 25 ppb and eosinophil count > 150 cells/μL versus the FeNO-low and eosinophil-high group (36%), which suggests that both biomarkers are synergistic in predicting response.[10] Something to note is that, whereas the patients in both FeNO groups were reported to have a blood eosinophil count of >150 cells/μL, a subsequent

analysis of the same data by Pavord *et al.*[22] in an abstract that showed that patients with a high FeNO level also had a higher mean eosinophil count (410–420 cells/μL) compared with the patients with lower FeNO levels (260–270 cells/μL), which may also be potentially confounding the noted difference. A *post hoc* analysis of the same study[11] also showed that patients with an FeNO value of ≥50 ppb had a 70% reduced risk of annual severe exacerbations on dupilumab compared with placebo. The reduction was lower, 56% and 21%, for the groups with FeNO of 25–50 ppb and < 25 ppb, respectively. The increase in FEV_1 was > 0.39 L in patients with FeNO values > 50 ppb on dupilumab compared with placebo; however, the change was substantially lower, at 0.12 L and 0.03 L for FeNO values between 25–50 ppb and < 25 ppb, respectively. These differences were present despite adjusting for potential confounders such as age, sex, height, baseline eosinophil count, *etc.*[11] It was also noted that FeNO levels did decline in patients started on dupilumab, as early as two weeks after initiation of the same. However, there was no significant association between the change in FeNO and rate of exacerbation, even though a reduced FeNO value was associated with improved lung function.[11] This may imply that, whereas the FeNO value may not be independently predictive of decreased exacerbation risk in patients on dupilumab, it may serve as a pharmacodynamic biomarker for dupilumab. Most of these analyses do not look at close interactions between the biomarkers but rather are a cross-sectional analyses of single markers, which suggests some caution in the conclusions drawn.

When looking at anti–IL-5/5R biologics, there is a limited role of FeNO in patients who are being started on these agents. In the DREAM study, a double-blind, placebo controlled study that randomized 621 patients, it was noted that treatment with mepolizumab, albeit effective at preventing exacerbations, did not affect the FeNO level.[12] Hearn *et al.*[23] also looked at the relationship between FeNO and the effectiveness of benralizumab and mepolizumab in a retrospective review and reported that there was no statistically significant association between baseline FeNO and the clinical effectiveness of these biologics. Therefore, it may not have a significant role in initiating patients on anti–IL-5 biologics or their subsequent monitoring.

As detailed above in the peripheral blood eosinophil count section, the patients on tezepelumab had annualized exacerbation reduction rates that were directly proportional to their baseline FeNO levels. As with dupilumab, tezepelumab was noted to cause reduction in FeNO levels with treatment, although the clinical significance of this reduction is uncertain.[16]

The changes in the biomarkers with biologics could just be reflective of the pharmacodynamic action because the FeNO level is driven by IL-4 and IL-13, which is targeted by dupilumab, and upstream by tezepelumab. Whereas eosinophils are driven by IL-5, not FeNO, this may explain the limited role of FeNO in patients on anti–IL-5 biologics, as discussed above.

Serum Total IgE

IgE levels are elevated in various atopic conditions, including asthma. Although there is no doubt that IgE plays a pivotal role in the pathophysiology of allergic and eosinophilic asthma, there is limited clinical relevance of checking the total IgE value as a biomarker in the management of the same. The serum total IgE level does not predict the response to biologics as established by several studies. Pooled analysis of seven omalizumab studies by Bousquet *et al.*[24] looked at patients with a wide range of IgE levels and reported that the patients benefited from the drug irrespective of their baseline IgE levels. This conclusion was also supported by the STELLAIR study by Humbert *et al.*[25] A *post hoc* meta-analysis of the MENSA[26] and MUSCA[27] trials on mepolizumab and pooled data from the SIROCCO and CALIMA trials on benralizumab also explored this further, with the results not supporting a predictive role for IgE in responsiveness to these biologics.[15,28] Similar trends were also noted in a *post hoc* analysis of QUEST study data for dupilumab.[29] Therefore, the utility of this biomarker is limited at this point of time. A cutoff IgE level of 30 IU/mL is, however, used to initiate omalizumab in patients with severe asthma, and the dose is calculated based on the body weight and serum IgE levels, with a higher dose or frequency administration being used for patients with higher IgE levels.[30] It is, however, challenging to monitor IgE levels in patients on omalizumab by using conventional IgE measurement methods because the binding of omalizumab to IgE can increase the half-life of IgE in human serum from 2.4 days to 26 days when complexed with omalizumab.[31]

Clinical Characteristics That Predict the Response to Biologics

Despite there being several biologics to choose from at this point, there is still not enough clarity on why patients respond to one biologic but not to another. It is, therefore, important to have a better understanding of what factors or comorbidities other than biomarkers can help predict a better response to a biologic. In a study on the Danish Severe Asthma Register Cohort by Hansen *et al.*[31] that investigated 501 patients who were started on biologics and reported that a lower body mass index was associated with a higher rate of clinical remission. Patients with a shorter duration of disease and less-severe disease were also more likely to achieve clinical remission.[31] Severe patients with asthma and with coexisting chronic rhinosinusitis with or without nasal polyposis or nasal polyposis alone

were noted to have a better response to biologics than patients without these comorbidities according to a large cohort study by Wechsler *et al.*[32] This was, however, not replicated in patients with asthma and with other atopic comorbidities such as atopic dermatitis or allergic rhinitis.[33] A study by Scelo *et al.*,[34] investigated prebiologic (anti–IgE, anti–IL-5/R, anti–IL4Ra) patient characteristics that predicted the treatment response in terms of various outcomes relevant to asthma. It was found that a history of allergic rhinitis was associated with a higher chance of having $\geq$ 50% dose reduction of oral corticosteroid from the prebiologic dose.[34]

In some cases, the presence of other coexisting indications that have evidence of benefit from a certain biologic may also guide the decision to choose one biologic over another in the management of asthma. For instance, in a patient with coexisting atopic dermatitis or chronic sinusitis with nasal polyposis, drugs with such dual indications may be preferable over the other biologic options. Similarly, mepolizumab and benralizumab are indicated for eosinophilic granulomatosis with polyangiitis, a vasculitic form of severe asthma. This drug class continues to gain additional indications, which is not the focus of this review.

CONCLUSION

Although there is no doubt that biomarkers have a role in the management and stratification of asthma, we must understand that there are several nuances to using them when evaluating a patient and when making decisions on the biologic of choice, and their subsequent monitoring. There are still substantial gaps in our knowledge of how these biomarkers should be reliably used in asthma management, and it is important to understand the limitations to avoid overestimating the extent of their utility. There is, unfortunately, no single perfect biomarker currently available that can be easily measured and can drive management decisions in all patients; therefore, further research is necessary to better understand the limitations and clinical utility of these biomarkers.

However, based on the available data, our approach is as follows. First, we obtain both the circulating eosinophil count and FeNO level to stratify the patient as either T2 high or low. As discussed, these baseline levels mostly predict a future exacerbation risk or are pharmacodynamic markers of the target being blocked rather than clearly differentiating one drug from another. If a patient is classified to have T2 low asthma, only tezepelumab is indicated for this category of asthma, and therefore becomes drug of choice. If circulating eosinophils are > 1500 cells/μL, then we tend to not use dupilumab when treating severe eosinophilic asthma because these patients were excluded from the phase III clinical trials. For this eosinophil-high group, any of the other four biologics (benralizumab, mepolizumab, omalizumab, or tezepelumab) would be an option because such subjects were studied in the registration programs. In this eosinophil-high group, the current biomarkers will not help differentiate a better outcome from one versus another for the reasons discussed in the article. The remaining patients whose eosinophil count ranged between 150 and 1500 cells/μL were included in the placebo controlled studies of all the biologics and have shown efficacy, leading to the approval of the biologics for this group. The latter group is the largest within the severe asthma cohort, and here we then factor in other characteristics for decision-making, such as comorbidities (drugs with multiple indications being preferred, depending on the comorbidity); dosing frequency, because benralizumab is the only drug that is currently dosed every 8 weeks, while the other biologics have a dosage frequency of 1–4 week; and any previous adverse events, in choosing the appropriate drug. Formulary availability and insurance approvals can also play a substantial role in the choice of biologic, despite following the thought process above, which must be factored into the decision.

REFERENCES

1. Enilari O, Sinha S. The global impact of asthma in adult populations. Ann Glob Health. 2019; 85:2.
2. Oppenheimer J, Hoyte FCL, Phipatanakul W, et al. Allergic and eosinophilic asthma in the era of biomarkers and biologics: similarities, differences and misconceptions. Ann Allergy Asthma Immunol. 2022; 129:169–180.
3. Bleecker ER, Meyers DA, Billheimer D, et al. Clinical implications of longitudinal blood eosinophil counts in patients with severe asthma. J Allergy Clin Immunol Pract. 2023; 11:1805–1813.
4. Bousquet J, Chanez P, Lacoste JY, et al. Eosinophilic inflammation in asthma. N Engl J Med. 1990; 323:1033–1039.
5. McBrien CN, Menzies-Gow A. The biology of eosinophils and their role in asthma. Front Med (Lausanne). 2017; 4:93.
6. Fowler SJ, Tavernier G, Niven R. High blood eosinophil counts predict sputum eosinophilia in patients with severe asthma. J Allergy Clin Immunol. 2015; 135:822–824.e2.
7. Hastie AT, Moore WC, Li H, et al. Biomarker surrogates do not accurately predict sputum eosinophil and neutrophil percentages in asthmatic subjects. J Allergy Clin Immunol. 2013; 132:72–80.
8. Korevaar DA, Westerhof GA, Wang J, et al. Diagnostic accuracy of minimally invasive markers for detection of airway eosinophilia in asthma: a systematic review and meta-analysis. Lancet Respir Med. 2015; 3:290–300.
9. Price DB, Rigazio A, Campbell JD, et al. Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study. Lancet Respir Med. 2015; 3:849–858.
10. Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. N Engl J Med. 2018; 378:2486–2496.
11. Pavord ID, Casale TB, Corren J, et al. Dupilumab reduces exacerbations independent of changes in biomarkers in moderate-to-severe asthma. J Allergy Clin Immunol Pract. 2024; 12:1763–1772.
12. Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet. 2012; 380:651–659.
13. Bleecker ER, FitzGerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-

agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. Lancet. 2016; 388:2115–2127.
14. FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2016; 388:2128–2141.
15. Jackson DJ, Humbert M, Hirsch I, et al. Ability of serum IgE concentration to predict exacerbation risk and benralizumab efficacy for patients with severe eosinophilic asthma. Adv Ther. 2020; 37:718–729.
16. Menzies-Gow A, Corren J, Bourdin A, et al. Tezepelumab in adults and adolescents with severe, uncontrolled asthma. N Engl J Med. 2021; 384:1800–1809.
17. Escamilla-Gil JM, Fernandez-Nieto M, Acevedo N. Understanding the cellular sources of the fractional exhaled nitric oxide (FeNO) and its role as a biomarker of type 2 inflammation in asthma. Biomed Res Int. 2022; 2022:5753524.
18. Couillard S, Shrimanker R, Chaudhuri R, et al. Fractional exhaled nitric oxide nonsuppression identifies corticosteroid-resistant type 2 signaling in severe asthma. Am J Respir Crit Care Med. 2021; 204:731–734.
19. Hanania NA, Wenzel S, Rosén K, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. Am J Respir Crit Care Med. 2013; 187:804–811.
20. Hanania NA, Alpan O, Hamilos DL, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. Ann Intern Med. 2011; 154:573–582.
21. Casale TB, Luskin AT, Busse W, et al. Omalizumab effectiveness by biomarker status in patients with asthma: evidence from PROSPERO, a prospective real-world study. J Allergy Clin Immunol Pract. 2019; 7:156–164.e1.
22. Pavord ID, Fitzgerald JM, Brusselle G, et al. Eur Resp J. 2019; 54 suppl 63. OA3807.
23. Hearn AP, Kavanagh J, d'Ancona G, et al. The relationship between Feno and effectiveness of mepolizumab and benralizumab in severe eosinophilic asthma. J Allergy Clin Immunol Pract. 2021; 9:92093–92096.e1.
24. Bousquet J, Rabe K, Humbert M, et al. Predicting and evaluating response to omalizumab in patients with severe allergic asthma. Respir Med. 2007; 101:1483–1492.
25. Humbert M, Taillé C, Mala L, et al. Omalizumab effectiveness in patients with severe allergic asthma according to blood eosinophil count: the STELLAIR study. Eur Respir J. 2018; 51:1702523.
26. Chupp GL, Bradford ES, Albers FC, et al. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. Lancet Respir Med. 2017; 5:390–400.
27. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med. 2014; 371:1198–1207. Erratum in: N Engl J Med. 2015; 372:1777.
28. Humbert M, Albers FC, Bratton DJ, et al. Effect of mepolizumab in severe eosinophilic asthma according to omalizumab eligibility. Respir Med. 2019; 154:69–75.
29. Corren J, Castro M, O'Riordan T, et al. Dupilumab efficacy in patients with uncontrolled, moderate-to-severe allergic asthma. J Allergy Clin Immunol Pract. 2020; 8:516–526.
30. US Food and Drug Administration. Xolair (omalizumab) highlights of prescribing information. Available online at https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/103976s5225lbl.pdf; accessed July 15, 2024.
31. Gon Y, Maruoka S, Mizumura K. Omalizumab and IgE in the control of severe allergic asthma. Front Pharmacol. 2022; 13:839011.
32. Hansen S, Baastrup Søndergaard M, von Bülow A, et al. Clinical response and remission in patients with severe asthma treated with biologic therapies. Chest. 2024; 165:253–266.
33. Wechsler ME, Scelo G, Larenas-Linnemann DES, et al. Association between T2-related comorbidities and effectiveness of biologics in severe asthma. Am J Respir Crit Care Med. 2024; 209:262–272.
34. Scelo G, Tran TN, Le TT, et al. Exploring definitions and predictors of response to biologics for severe asthma. J Allergy Clin Immunol Pract. 2024; 12:2347–2361. □